Comparison of Minimal Phototoxic Dose and Skin Type for Determining Initial UVA Dose in Oral Liquid Methoxsalen Photochemotherapy for the Treatment of Psoriasis

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Twenty-five patients with extensive psoriasis were randomly assigned into one of three groups, each receiving 0.5 mg/kg of oral liquid methoxsalen photochemotherapy followed 1 h later by exposure to long-wave ultraviolet light (UVA). The sole difference between the three groups was the method used to determine the initial UVA dose, which was either based on skin type, 25% of the minimal phototoxic dose (MPD), or 50% of the MPD.

All patients were treated in the Phototherapy Unit at the Massachusetts General Hospital. Data were obtained until reaching the endpoint of clearance. At clearance, the results of the number of treatments required to clear, final UVA dose, cumulative UVA dose, and side effects were tabulated, compared, and analyzed for each of the three groups.

The 25% and 50% MPD groups required a mean of 15.0 ± 1.7 and 13.4 ± 1.9 treatments to clear, respectively, as compared to the skin type group, which needed an average of 17.6 ± 2.5 treatments. The mean final UVA dose was 7.4 ± 0.9 J/cm^2 and 8.4 ± 1.4 J/cm^2 for the 25% and 50% MPD groups, respectively, in contrast to 11.6 ± 1.4 J/cm^2 for the skin type group. The mean cumulative UVA dose at clearance for the 25% and 50% MPD groups was 79 ± 16 J/cm^2 and 87 ± 27 J/cm^2, respectively, versus 136 ± 30 J/cm^2 for the skin type group. The comparisons between the individual MPD groups and the skin type group did not achieve statistical significance with the exception of a marginally significant difference in final dose between the skin type group and the 25% MPD group ($p = 0.06$). However, the results of the two MPD groups were then pooled and the mean final (7.9 ± 0.8 J/cm^2) and cumulative (83 ± 15 J/cm^2) UVA doses were significantly ($p = 0.04$) and marginally significantly ($p = 0.07$) lower than the respective means of the skin type group. The number of treatments to clear, although lower in the pooled MPD groups (14.2 ± 1.3) than in the skin type group, did not attain statistical significance ($p = 0.19$).

Our data suggest that the MPD measurement may be superior to the skin-typing system when calculating the initial UVA dose in oral liquid methoxsalen photochemotherapy for the treatment of psoriasis. *J Invest Dermatol 97:1048–1052, 1991*

Psoralen-induced photosensitivity varies considerably among patients [1–8]. Consequently, in PUVA (psoralen plus UVA), a given dose of UVA will cause an erythema and pigmentation response of considerable variation among patients. It is imperative then to accurately gauge an individual's degree of psoralen photosensitivity prior to the initiation of PUVA. Traditionally, this determination has been based either on an individual's skin type or on the minimal phototoxic dose (MPD). Both methods have been successful. However, no clinical trials have been conducted to establish whether one method is superior. The purpose of this protocol was to demonstrate whether one method presently used for determining the initial UVA dosage is better than the other.

Manuscript received February 20, 1991; accepted for publication July 31, 1991.

Presented in part at the Forty-Ninth Annual Meeting of the American Academy of Dermatology, Atlanta, Georgia, December 1–6, 1990.

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MATERIALS AND METHODS

Patients Twenty-five psoriatic patients participated in this clinical trial. There were 10 women and 15 men. The age of the subjects ranged from 24 to 80 years; the mean age was 51 years. The mean duration of psoriasis was 15 years with a minimum and maximum of 1 and 55 years, respectively. One patient had been successfully treated with methotrexate on previous occasions. No other systemic agents had been employed during or prior to the study. Sixteen patients were previously treated with UVB therapy (12 were non-responders and four were responders). Fourteen patients were previously treated with PUVA therapy (three were non-responders and 11 were responders).

All patients had severe psoriasis that had failed to respond to conventional topical therapy. At the initiation of the study, the patient's psoriasis was either stable or flaring. All patients had generalized plaque psoriasis except for two patients, one of whom had

0022-202X/91/$03.50

guttate psoriasis and the other had erythrodermic psoriasis. Patients with pustular psoriasis were excluded from the study.

None of the patients received any systemic cytotoxic agents or retinoids for at least 1 month before starting treatment. Other exclusions for entry into the study were patients who had received PUVA within 2 months of admission to the protocol or UVB within 1 month. During the course of treatment, no topical medications were used, except for emollients, on areas exposed to PUVA. Most patients received topical medications to the scalp and/or intertriginous regions.

Prior to the initiation of therapy, the protocol as well as the potential side effects of the treatment were carefully explained to the patient. A signed informed consent was obtained in each case.

Drug Liquid 8-methoxypsoralen (Oxsoralen-Ultra) in 10-mg soft gelatin capsules was administered to each patient 1 h prior to UVA exposure. The medication is manufactured by Elder Pharmaceuticals, Inc., Costa Mesa, CA. According to body weight, psoralen doses of 0.5 mg/kg were calculated for each participant.

UV Source The source of ultraviolet radiation was an Ultralite V4472-IV UVA unit emitting a continuous spectrum between 320 and 400 nm, peaking at 365 nm. The average irradiance of the source was 25–35 mW/cm^2.

Skin Typing A system of skin typing was originally proposed by Fitzpatrick in 1975 [9], later modified by Pathak et al in 1976 [10] and used by Melski et al in a cooperative clinical trial in 1977 [11]. In this protocol, a short personal interview on each patient's sunburning and suntanning history was obtained as well as a physical assessment of skin pigmentation. This skin-typing system accomplished the purpose of determining a patient's sensitivity to UV light. Classification of skin types I–IV was based on a patient's history of typical response to an initial 45–60 min of noon sun exposure in early summer. Patients were categorized as skin type V and VI by the clinical appearance of the skin.

The percent of patients in each of the six skin types in the present study closely parallels the results of the cooperative studies by Melski et al [11] and Henseler et al [12]. In all three protocols, more than half of the patients were skin type III with second and third place going to skin types II and IV, respectively.

Phototesting In addition to skin typing, phototesting was utilized in this study to estimate an individual's sensitivity to UV light. Thus, the MPD, which represents the patient's threshold sensitivity to PUVA, was determined for all participants. The MPD is defined as the dose of UV radiation needed to produce 1+ erythema (minimal uniform erythema with clearly defined borders) after ingestion of drug and exposure to UV radiation [13,14].

One hour after ingestion of methoxsalen, eight 2 × 2 cm template square test fields were irradiated with increasing doses of UVA (2, 4, 6, 8, 10, 12, 14, and 16 J/cm^2), whereas the remainder of the body was covered. The degree of erythema and pigmentation was graded at 48 and 72 h after irradiation by at least two experienced observers, who were unaware to which one of the three groups the patient was allocated. The 72-h reading was the one used in all final calculations, using a 1+ to 5+ scale to determine the MPD (Table I) [14]. The mean MPD of the patients was 8.0 J/cm^2, with a range of 4.0 to 14.0 J/cm^2.

Trial Design The MPD and skin type for each patient was determined prior to the initiation of therapy according to the above methods. The investigation was accomplished prospectively in a double-blind fashion. The investigators and patient were unaware to which group the patient had been assigned. A total of 25 ambulatory, psoriatic patients from the Phototherapy Unit at the Massachusetts General Hospital were randomly placed into one of three groups. There was no difference in the overall distribution of skin type (Table II, $p = 0.75$) or of severity of psoriasis as assessed by the total body surface area affected by psoriatic plaques ($p > 0.6$). Each group was treated 3 d per week with at least 48 h between successive treatments. The dose of UVA radiation was increased in each treatment by 0.5–1.0 J/cm^2 as long as there was no or very minimal erythema from the previous treatment. If a minimal to moderate erythema was present, the dose of UVA radiation was held constant. If the patient experienced a definite or subjectively tender erythema, the patient was not treated on that occasion.

Table I. Scale for Grading Erythema and Pigmentation [14][a]

Scale	Degree of Erythema	Scale	Degree of Pigmentation
0	No erythema	0	No change in basic skin color
1	Minimal perceptible erythema	1	Minimal perceptible tan
2	Light pink erythema	2	Light-brown pigmentation
3	Marked erythema, red in color, but no edema	3	Moderate to medium brown pigmentation
4	Fiery red erythema with edema and tenderness	4	Dark brown pigmentation
5	Violaceous red erythema, blistering and tenderness	5	Intense deep brown or black pigmentation

[a] Scales 1 to 5 should have clearly defined borders.

All patients received oral liquid methoxsalen (0.5 mg/kg) followed 1 h later by UVA exposure, which was delivered in exactly the same fashion to all patients. The only difference between the three groups was the method used to determine the initial UVA dose, which was as follows: group A, based on skin type; group B, 25% MPD; group C, 50% MPD.

For Group A, the skin type was used for determining the first treatment exposure dose of UVA. On subsequent exposures, dose increments of 0.5 or 1.0 J/cm^2 were employed, also determined by skin type. The initial and incremental UVA doses (J/cm^2) for this group of patients are shown in Table III. All patients received additional UVA exposures to the extremities, beginning on the second treatment. The initial and incremental UVA dose to the extremities was also based on skin type, as delineated in Table III.

For groups B and C, the MPD was used to determine the initial UVA dose. The first exposure doses of UVA were 25% and 50% of the MPD for groups B and C, respectively. The increments in UVA dosage to the total body as well as the initial and incremental dosages to the extremities were determined according to the skin type as in group A (Table III).

When clearance was achieved, the dose of UVA was held constant. Patients were considered to be clear when 95% of the originally involved, treated areas were devoid of erythema, scaling, and palpability. After clearance, the number of treatments to clear, cumulative UVA dose, final UVA dose, and side effects were statistically compared for each group. Finally, based on this data, an evaluation was made as to whether significant differences exist between each group regarding the above parameters.

Data Collection A standard, investigator-administered (ER) questionnaire was completed by the patient during the initial personal interview. At this time, a complete skin examination was performed and photographs were taken. The patient had frequent

Table II. Distribution of Skin Type

Skin Type	Group A (skin type) n = 9	Group B (25% MPD) n = 8	Group C (50% MPD) n = 8
I	0	0	1
II	2	1	2
III	5	7	4
IV	2	0	0
V	0	0	1
VI	0	0	0

Table III. Initial UVA Dose for PUVA Therapy and Dose Increments for Each Treatment Based on Skin-Typing System

	UVA Dose (J/cm²) to Total Body		Additional UVA Dose (J/cm²) to Extremities	
Skin Type	Initial	Increments	Initial[a]	Increments
I	1.0	0.5	0.5	0.5
II	2.0	0.5	0.5	0.5
III	3.0	0.5	1.0	0.5
IV	4.0	1.0	1.0	1.0
V	5.0	1.0	1.0	1.0
VI	6.0	1.0	1.0	1.0

[a] Initial UVA dose to extremities: start on second treatment if needed.

physical examinations of the skin in order to monitor the clinical response and side effects. Detailed, daily progress notes were taken on all patients. The initial laboratory data included a complete blood count, urinalysis, antinuclear antibodies, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, glutamic oxalacetic transaminase, and lactic dehydrogenase. A complete opthalmologic examination was also required.

Statistics Cumulative dose, final dose, and the number of treatments required for clearance among the three groups were compared and analyzed with a one-way analysis of variance followed with Scheffé-type contrasts for pairwise comparisons. To test the more general hypothesis of whether the MPD method is better or worse than the skin type method, the two MPD treatment groups were compared collectively with the skin type group using an appropriate orthogonal contrast.

Data are summarized as means ± 1 standard error of the mean. Prior to analysis, the data were transformed to a logarithmic scale to equalize the variances among groups. Analyses were performed with the use of MIDAS (Michigan Interactive Data Analysis System), a statistical software package developed by the Statistical Research Laboratory at the University of Michigan.

RESULTS

All patients experienced degrees of clearance ranging from 95% to 100%. The mean number of treatments to clear was 15.4 ± 1.2, with a mean cumulative UVA dose of 102.1 ± 15.2 and a final UVA dose of 9.2 ± 0.8 J/cm² for all groups combined.

The 25% and 50% MPD groups required a mean of 15.0 ± 1.7 and 13.4 ± 1.9 treatments to clear, respectively, as compared to the skin type group, which needed an average of 17.6 ± 2.5 treatments (Fig 1). The mean cumulative UVA dose at clearance for the 25% and 50% MPD groups was 79 ± 16 J/cm² and 87 ± 27 J/cm², respectively, versus 136 ± 30 J/cm² for the skin type group (Fig 2). The mean final UVA dose was 7.4 ± 0.9 J/cm² and 8.4 ± 1.4 J/cm² for the 25% and 50% MPD groups, respectively, in contrast to 11.6 ± 1.4 J/cm² for the skin type group (Fig 3).

The data showed that the two groups in which the starting dose was derived from the MPD, as compared to the skin type group, required a fewer number of treatments to clear and a lower UVA exposure in terms of the cumulative and final dose. Because the results of the two MPD groups were not consistently statistically significant, they were pooled and then compared to the skin type group. The results of the combined MPD groups revealed a borderline significant ($p = 0.07$) mean cumulative UVA dose (83 ± 15 J/cm²) and a statistically significant ($p = 0.04$) mean final UVA dose (7.9 ± 0.8) when compared to the aforementioned results of the skin type group (Figs 2 and 3).

In summary, in terms of the mean final and cumulative UVA doses at clearance, the pooled MPD groups cleared with less (significant and marginally significant, respectively) UVA exposure than the skin type group.

Nausea, erythema, light-headedness, headache, and pruritus were the most common acute side effects reported in this study. Although some adverse reactions were not rare, they occurred in only a small percentage of the treatments and were usually mild and transient. Erythema was observed in 32% of the patients, 16% of whom experienced minimal to moderate erythema, resulting in holding the UVA dose constant. Severe erythema accompanied by edema and/or tenderness, causing a missed treatment, was reported by 12% of

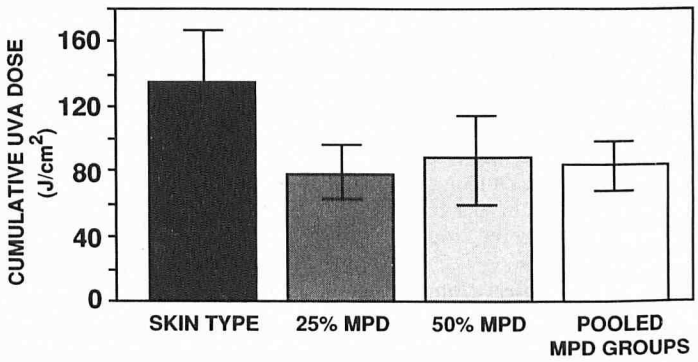

Figure 2. Mean cumulative UVA dose at clearance: a comparison of skin type (n = 9) versus 25% MPD (n = 8, p = 0.12), 50% MPD (n = 8, p = 0.12), and pooled MPD groups (n = 16, p = 0.07) for determining initial UVA dose. *Bars,* means ± SEM; ANOVA with Scheffé contrasts.

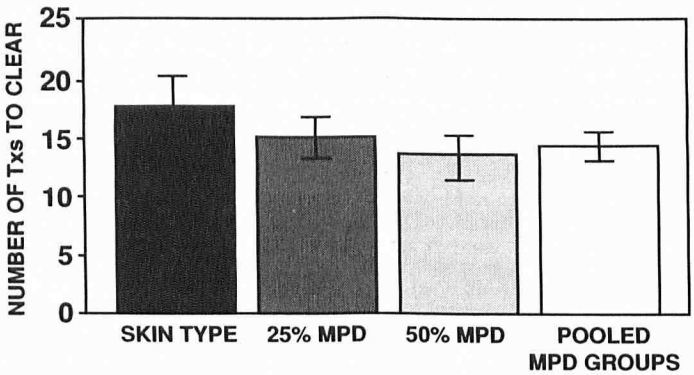

Figure 1. Mean number of treatments required for clearance: a comparison of skin type (n = 9) versus 25% MPD (n = 8, p = 0.43), 50% MPD (n = 8, p = 0.15), and pooled MPD groups (n = 16, p = 0.19) for determining initial UVA dose. *Bars,* means ± SEM; ANOVA with Scheffé contrasts.

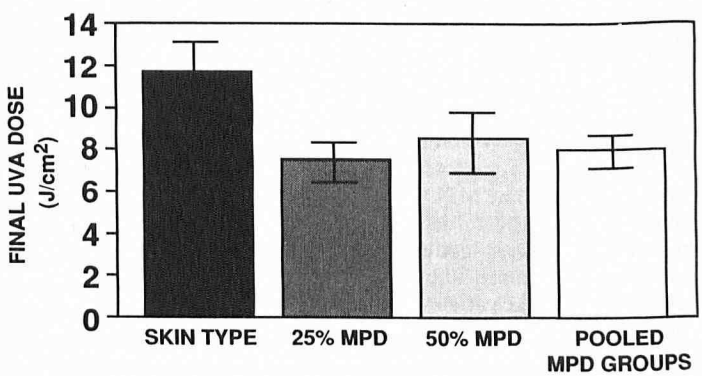

Figure 3. Mean final UVA dose at clearance: a comparison of skin type (n = 9) versus 25% MPD (n = 8, p = 0.06), 50% MPD (n = 8, p = 0.10), and pooled MPD groups (n = 16, p = 0.04) for determining initial UVA dose. *Bars,* means ± SEM; ANOVA with Scheffé contrasts.

Table IV. Comparison between US, European, and Present Study

	U.S. [11]	European [12]	Present
Number of treatments	20.3	20.0	15.4
Final dose (J/cm²)	14.0		9.2
Cumulative dose (J/cm²)	249.0	96.0	102.1

the patients. One patient noted localized blisters, necessitating shielding of this area. Statistically, there was no significant difference among the three groups with respect to severity or quantity of erythema. Laboratory tests, performed in all 25 patients, showed no abnormalities that could have been attributed to PUVA.

DISCUSSION

The results of this study of 25 psoriatic patients treated with PUVA therapy suggest that the MPD measurement may be superior to skin typing for determining the initial UVA dose. Larger, preferably multicenter studies, should be performed in order to confirm or challenge our results.

There have been several large clinical trials in the United States utilizing the system of skin typing to determine the initial UVA dose in oral methoxsalen photochemotherapy for psoriasis [11,15]. In these protocols, skin typing appeared to serve a useful purpose. Wilson et al [16] found considerable homogeneity of MED values within skin types I and IV, which further supported the method of skin typing. Skin typing has the advantages of being simpler and quicker; it may be the method of choice for determining the initial UVA dose for patients with skin types V and VI because the MPD is sometimes difficult or impossible to determine in these individuals.

However, the great majority of investigators believe, as we do, that the MPD measurement is superior to skin type when calculating the initial UVA dose in PUVA therapy. Many dermatologists, especially in Europe, prefer sensitivity testing to skin typing [17]. Wolff et al [16] were the first group to propose that the best way to determine the initial UVA dose in PUVA therapy is by doing an MPD measurement. Henseler et al [12] in the European PUVA study used phototoxicity testing to determine the starting dose in nearly half of the patients, resulting in clearing of psoriatic lesions with a decreased total cumulative UVA dose. Stern and Momtaz [3] reported that although skin type was a good clinical predictor of skin cancer, it lacked specificity as an estimator of an individual's MPD. Several other authors have demonstrated a wide variation in MPD or MED values within a particular skin type [19–23]. Moreover, Fitzpatrick, who conceptualized the "Fitzpatrick skin typing system" [9], recently published an editorial that agreed that the MPD is better than skin type for this purpose and stated that the use of the MPD for the selection of the initial UVA dose is now the standard practice in the PUVA clinic at the Massachusetts General Hospital [4]. As both skin typing and sensitivity testing have advantages and disadvantages, perhaps the best approach would be a combination of the two methods.

The results of the present study were compared with those of the U.S. [11] and European [12] Cooperative studies in terms of the mean number of treatments required for clearing, final UVA dose, and cumulative UVA dose (Table IV). In the present study, patients cleared with a mean of 15 treatments versus 20 treatments in both cooperative studies. Furthermore, the present study reported significantly decreased mean final and cumulative UVA doses, as compared to the United States and European trials, with the exception of the comparison between the cumulative doses in the European and present study, which were not statistically different (Table IV). One explanation for the lower UVA exposure in the present study as compared to the United States and European trials is that the former study employed the liquid preparation of 8-methoxypsoralen and the latter two trials used the crystalline form. Hönigsmann et al [2] reported a significant reduction in the UVA dose required for clearing psoriasis with the liquid preparation of methoxsalen.

The significance of lowering the total UVA energy requirements for clearing psoriasis during PUVA therapy is not entirely known, but this is often one of the goals of this treatment. Many long-term side effects of PUVA therapy may have long latent periods; therefore, it is imperative that more studies are performed to adequately determine these risks. Non-melanoma skin cancer is the main long-term risk of PUVA therapy, and this is dose dependent [24]. In contrast, no clear relationship was noted betweeen PUVA exposure and tumor development in the follow-up of 1643 patients for an average of 96 months in the European study [25]. In order to diminish the long-term side effects of prolonged PUVA therapy, it is necessary to accurately estimate the initial UVA dose in order to clear the patient at decreased UVA doses.

We are very grateful to Patty Falls, Laura Van Goor, and the phototherapy technicians at the Massachusetts General Hospital for invaluable assistance.

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